

□ Liquid Biopsy for Intracranial Metastases Diagnosis

“A drop of fluid may now say what a scalpel once had to prove.”

□ Definition

Liquid biopsy is a minimally invasive method to detect tumor-derived biomarkers (ctDNA, CTCs, exosomes, microRNA) in body fluids—especially **cerebrospinal fluid (CSF)** or **blood**—to characterize and monitor **intracranial metastases**.

□ Clinical Purpose

- Molecular diagnosis when tissue biopsy is risky or contraindicated
- Identification of targetable mutations (e.g. EGFR, ALK, BRAF)
- Monitoring of treatment response and resistance
- Differentiation between tumor recurrence and radiation necrosis

□ Source Comparison

Feature	CSF	Plasma
Proximity to brain lesion	□ Direct contact	□ Indirect
ctDNA yield in CNS disease	□ High	□ Low in brain-only mets
Invasiveness	□ Lumbar puncture required	□ Peripheral blood
Diagnostic sensitivity	□ Especially in leptomeningeal	□ Limited in CNS-only

□ Biomarkers Detected

- Circulating tumor DNA (ctDNA)
- Circulating tumor cells (CTCs)
- Exosomal RNA and microRNA
- Tumor-specific mutations (e.g. EGFR T790M, ALK fusions)

⚙ Platforms and Technologies

- Digital PCR
- Next-Generation Sequencing (NGS)
- BEAMing
- Droplet Digital PCR (ddPCR)

⚖️ Advantages

- Non-invasive or minimally invasive
- Repeatable for longitudinal monitoring
- Captures tumor heterogeneity
- Useful when lesion is deep, multifocal, or previously irradiated

❏ Limitations

- Low yield in plasma for brain-only metastases
- Requires lumbar puncture for CSF
- False negatives in necrotic or treated lesions
- Currently not standard of care in all centers

❏ Relevance to Neurosurgery

- When tissue biopsy is **inaccessible, unsafe, or non-diagnostic**
- For molecular stratification in patients with **progressive or recurrent brain metastases**
- As a tool for **non-invasive follow-up** in high-risk or medically fragile patients

❏ Current Role

- Adjunct to imaging and clinical evaluation
- Supports precision oncology decisions
- Still under validation for routine neurosurgical practice

Reviews

A review of Hongsermeier-Graves et al. ¹⁾ purports to explore the role of **liquid biopsy in the early detection and monitoring of central nervous system (CNS) metastases**, aligning itself with the [precision medicine](#) zeitgeist. The abstract recycles generic platitudes about tumor heterogeneity, genomic annotation, and immunotherapy response without offering CNS-specific insight.

⚠️ Fundamental Weaknesses

❏ 1. The CNS Is Not Just “Another Site”

Despite its title, the article treats CNS metastases as merely another metastatic niche. There is **no meaningful exploration of the blood-brain barrier**, the critical distinction between **CSF and plasma-based detection**, or the **challenges of ctDNA shedding in isolated CNS lesions**. These

omissions are glaring for a paper claiming to address **CNS-specific diagnostic tools**.

□ 2. Incoherent Structure and Overstuffed Generalities

The article reads like a **compilation of PubMed alerts**—a bloated medley of genomic buzzwords (EGFR, ALK, NGS, immunotherapy, resistance mutations) without structure, depth, or hierarchy. The authors oscillate between **basic oncology reviews** and **surface-level CNS mentions**, failing to deliver focused analysis or original synthesis.

□ 3. Decorative Neuroscience

Any mention of CNS-specific context (e.g., [leptomeningeal disease](#), [radiation necrosis](#)) is **decorative**—mentioned briefly and then forgotten. The review indulges in **academic name-dropping** of promising technologies (like droplet digital PCR or methylation profiling) without critically addressing their limitations in CSF, such as low sensitivity in low-volume samples or contamination by peripheral blood DNA.

□ 4. Algorithmic Vanity

The paper worships “[precision medicine](#)” in the abstract sense, showcasing **algorithmic vanity**—pretending complexity and future-readiness by merely citing [machine learning](#) or “real-time genomic tracking” without concrete application in the neuro-oncological setting.

□ 5. Statistical Irrelevance

The review lacks quantitative backbone: there’s **no discussion of sensitivity, specificity, PPV/NPV, or comparative metrics** of liquid biopsy versus gold standards (surgical biopsy, MRI, CSF cytology). It’s all theoretical promises—**no performance benchmarks, no validation studies**.

□ Neurosurgical Irrelevance

For the neurosurgeon, this paper is **epistemological fluff**: it provides no decision-making guidance, no workflow integration, and no criteria for when or how [liquid biopsy](#) is truly actionable in CNS metastatic patients. It romanticizes “[monitoring](#)” without specifying **how** results would change neurosurgical or neuro-oncological management.

□ Academic Marketing Pamphlet

Ultimately, the review functions more as a **marketing pamphlet for liquid biopsy platforms** than a critical appraisal of current clinical utility. It smacks of **sponsored optimism**, designed to **attract citations and institutional funding**, not to educate clinicians who face the daily ambiguity of treating brain metastases.

❏ Final Verdict

- **Decorative:** CNS mentioned only enough to justify the title.
- **Redundant:** Most content applies generically to oncology, not neuro-oncology.
- **Uncritical:** No meaningful discussion of limitations, false positives/negatives, or failed trials.
- **Useless:** No algorithm, no guidance, no translational bridge to clinical practice.

This is not a [review](#). It's a genomic TED talk in disguise.

[Liquid biopsy](#) collect and analyze tumor components in body fluids, and there is an increasing interest in the investigation of liquid biopsies as a surrogate for [tumor tissue](#) in the management of both primary and secondary brain tumors.

Boire et al., critically reviewed available literature on spinal fluid and plasma circulating tumor cells (CTCs) and cell-free tumor (ctDNA) for diagnosis and monitoring of leptomeningeal and parenchymal brain metastases. We discuss technical issues and propose several potential applications of liquid biopsies in different clinical settings, i.e. for initial diagnosis, for assessment during treatment and for guidance of treatment decisions. Last, ongoing clinical studies on CNS metastases, that include liquid biopsies, are summarized and recommendations for future clinical studies are provided ²⁾.

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¹⁾

Hongsermeier-Graves N, Hasen M, Yaffe N, Ajisebutu A, Malani R. Liquid biopsy in early detection and monitoring of CNS metastases. Adv Cancer Res. 2025;165:255-290. doi: 10.1016/bs.acr.2025.04.007. Epub 2025 May 21. PMID: 40518192.

²⁾ ³⁾

Boire A, Brandsma D, Brastianos PK, Le Rhun E, Ahluwalia M, Junk L, Glantz M, Groves MD, Lee EQ, Lin N, Raizer J, Rudà R, Weller M, van den Bent MJ, Vogelbaum MA, Chang S, Wen PY, Soffietti R. Liquid biopsy in Central Nervous System metastases: a RANO review and proposals for clinical applications. Neuro Oncol. 2019 Jan 22. doi: 10.1093/neuonc/noz012. [Epub ahead of print] PubMed PMID: 30668804.

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